Unanswered questions concerning antibiotic resistance

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Given the constant anguish of the popular press about the forthcoming onslaught of 'andromeda strains' which will bring an end to the golden age of antibiotics, the multi-resistant microbial pathogens refractory to all forms of treatment, one might wonder what remains mysterious about antibiotic resistance? Pharmaceutical companies, the medical community, and countless researchers world-wide have been aware of the problem of antibiotic resistance for nearly fifty years and many papers have been written on the subject; surely everything is known about this phenomenon! Surprisingly (and perhaps sadly) the answer is no, the reason being that, while certain aspects of antibiotic resistance are well characterized, many essential facts concerning the genetic ecology of antibiotic resistance are poorly understood. Microbial antibiotic resistance (as we know it) is the result of exorbitant antibiotic usage over the past half-century. It is clear that much of this use is, at best, inappropriate. Only half of the world production of antibiotics goes into human therapy, the remainder is employed in agriculture, aquaculture, animal husbandry, and the like. However, it is too late to lay blame – we cannot turn back the clock. Responsibility for loss of clinical effectiveness due to the development of antibiotic resistance must be borne by all.

What more do we need to know about the subject? Following the introduction of antibiotics into therapeutic use, microbes developed resistance very rapidly, and although chromosomal mutations are likely to have played an important role in the initial steps, the major route by which bacteria became resistant was gene acquisition, principally from antibiotic-producing organisms in the environment, but most probably from other microbial sources as well. All well and good, but *what* microbes first inherited the resistance genes? The original beneficiaries of the natural exchange of resistance genes – Gram-positive, Gram-negative, cultivatable, non-cultivatable, pathogen or non-pathogen – cannot be identified. The initial events cannot be re-created. Plausible genetic mechanisms for the 'pick-up' of resistance genes have been identified for some microbial species, but not all. The available evidence suggests that the pattern of resistance gene flow was from Gram-positive to Gram-negative bacteria, but the mechanisms of prior acquisition by the Gram-positives is unknown. And what of dissemination? Did this take place by one or several different mechanisms, and pathways, before reaching the current Gram-negative pathogens? How many inter-generic and inter-specific transfers through how many different hosts were required? There are great gaps in the understanding of these processes. What promotes dissemination? What are the routes of dissemination of resistance genes from the microbial populations of animals to humans, or humans to animals or fish? Unfortunately, the opportunity to carry out definitive studies of the origins and development of antibiotic resistance has been missed, since most examination of the origins and dissemination of antibiotic resistance must be retrospective, long after the event in microbial terms, and the exact scenarios are difficult to reproduce.

Were this information available we would be in a better position to evaluate the implications of the use of antibiotics as animal growth promotants or fish food and the contribution of non-human use of antibiotics to the overall problem of development and spread of resistance. In addition, do we know the real economic benefits of antibiotic use in agriculture and aquaculture? Are existing practices truly effective and have alternatives been investigated? Given that the whole process is so multi-functional, from the point of view of genetics and biochemistry as well as in terms of the economics of animal husbandry, etc., is there time to re-evaluate every aspect of antibiotic usage before it creates a health, environmental, and economic disaster?

Realistically, all antibiotic therapy must be considered in the context of the inevitable – resistance to any drug will develop sooner or later. Can one hope for the introduction of practices that make it later? How can we delay this inevitability without a better understanding of the biological processes involved? Filling in the gaps in our knowledge of how microbes become resistant to antibiotics might give us better ideas of how to combat the overall problem. There is a need to expand our understanding of the basic microbial genetic ecology involved. This requires much more fundamental research, but who will (should) pay for this? Everyone! All users and abusers and their regulatory agencies (pharmaceutical companies, agricultural feed companies, appropriate government departments, and the public) have a vested interest in maintaining the efficacy of antibiotics.

New antibiotics are coming along and the pharmaceutical industry needs to recoup its extensive investment in research and development. However, one would hope that introduction of the next major antibiotic class (soon and several, we hope) will be governed by increasing awareness and comprehension

of the negative aspects of antibiotic use. The 'new' antibiotics must be dispensed prudently for human therapy, regulated by clinicians, pharmacists, etc., with the knowledge that departure from such regimes will convert valuable drugs into a plethora of 'me-toos' in a constant chemical battle to keep ahead of the microbes.

Antibiotic discovery and subsequent use is changing. The enormous efforts in genomic analysis of bacterial pathogens will undoubtedly identify many new drug targets; in a few years time the nucleotide sequence of the genomes of most pathogens will be known. The most obvious result of this effort will be pathogen-specific inhibitors. The controlled use of narrow-spectrum (or niche-specific) antibiotics in the place of random use of broad-spectrum agents is surely one way to reduce the global problem of antibiotic resistance. For this to be implemented, accurate clinical and microbiological diagnosis will be a required adjunct to antibiotic prescription and is likely to be expensive. Will this paradigm change be accepted by pharmaceutical marketing divisions, the medical profession, HMOs? Can we count on a corresponding development of rapid, automated diagnostic technology needed to make the best use of drugs active against specific bacterial species? Everything done up to now has been 'damage control' – a knee jerk reaction to something that has happened. Is it not time to be prospective instead of retrospective?

Only when the mysteries of the evolution of resistance, the efficacy of present practices, and the economics of drug discovery and use are resolved will it be possible to envisage the future of antibiotics in the treatment of infectious disease. Ironically, a similar viewpoint was stated 40 years ago by Sir Charles Harington in his introductory remarks to a CIBA Foundation Symposium on Drug Resistance in Micro-Organisms:

We cannot be sure that the searchers for new drugs and antibiotics will always win the race. However hard and successfully we may work in the search for new drugs we shall therefore continue to labour under discouragement so long as we are faced with the bugbear of drug resistance. The problem is one of microbial biochemistry, physiology and genetics, and can only be solved by work in these fields. Until we understand the problem we shall have no hope of overcoming it, and until we overcome it we shall have no real sense of security in our chemotherapy. The subject . . . is not only of the greatest scientific interest and importance; it has also a background of practical medical urgency.

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It would seem that no one was really listening!

Julian Davies
Department of Microbiology,
University of British Columbia,
Vancouver, BC